

no doubt, was due to the virulence of the streptococci used, as most of the animals died within a period of a few days following the treatment. It may also be indicated that the striking feature in these animals was not the joint involvement but rather a picture of severe infection characterized by extensive hemorrhages.

At the time when the experiments were being conducted with the streptococcus from the submaxillary gland, twenty-five rabbits were used for controls. Fifteen rabbits were treated with hemolytic streptococci from pleural fluid. Five rabbits each were treated respectively with two strains of *S. pyogenes* and five rabbits received injections of a *S. subacidus*. Ten other rabbits were inoculated in series of five with two strains of *S. pyogenes* that were isolated respectively from a herniotomy wound and peritoneal exudate. The results obtained in these animals were in marked contrast to those animals inoculated with the streptococcus from the submaxillary gland in that they presented a hemorrhagic type of reaction similar to that which we had previously reported. These animals were from our own stock and apparently in identical physical condition. The doses administered to these animals were not excessive in that 1.5 c.c. were given to twenty rabbits and 2 c.c. to five rabbits. From these results it would appear that the qualities of this particular streptococcus are somewhat different from others which we have studied. It is difficult to understand why a streptococcus isolated from a human submaxillary gland should have a predilection for the joints of rabbits. It would seem that although this streptococcus showed a remarkable constancy in location and type of lesion produced, the location of the lesions in the animal had no relation to the origin of the organism or to the lesion produced by it in the patient from which the strain was obtained. Results of this kind limit the usefulness of experimental bacteriology for determining a possible tissue predilection for organisms of human origin.

**Conclusions.** From our study of this organism it would appear that we have a streptococcus of fairly low pathogenicity but of rather high invasive quality, which possesses the ability to attack the joints of rabbits and produce in them a chronic suppurative arthritis. This quality of attacking the joints was not lost after a period of three months' artificial cultivation. Although joints were mainly attacked, certain other tissues were involved an appreciable number of times. The organism was of human source, isolated from the submaxillary gland.

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## BLOOD CHOLESTEROL IN GASTRO-ENTEROLOGIC CASES.<sup>1</sup>

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CHOLESTEROL or cholesterin, a monatomic alcohol, is found as such in the human blood stream. In combination with fatty acids it forms, among other esters, cholesterol palmitate and cholesterol oleate. A fairly definite relation or balance is maintained between the free and combined cholesterol of the blood. Cholesterin is also found in the nervous system, bile, milk and other body tissues and fluids. There is some uncertainty as to the exact chemical structure of cholesterol.<sup>2</sup> It is soluble in ether, chloroform, benzene, fats and hot alcohol.

The origin of cholesterol is, for the most part, exogenous, although there is some evidence that it may have an endogenous source.<sup>3</sup> It is readily absorbed from the intestinal tract contents through the chyle and may be recognized free or esterized in the contents of the thoracic duct.<sup>4</sup> The blood cholesterol content can be readily increased by feeding foods rich in this substance. That the biliary cholesterol can be increased in like manner remains uncertain. Feeding experiments leave this point in doubt. The origin of biliary cholesterol is perhaps to be found in the disintegrating blood cells of the body. Bile is the only suitable solvent in the body for cholesterol, but whether the bile is a normal mode of excretion for this substance is just as uncertain as other facts pertaining to this alcohol. Fistula bile is poorer in cholesterol than gall-bladder bile, and some, therefore, believe that this substance somehow or other has its origin in the lining membrane of this organ. Some contend that this difference in the bile from these two sources soon ends after the unusual conditions imposed by the operation cease;<sup>5</sup> recently, Rous and McMaster<sup>6</sup> seem to have demonstrated an ability on the part

<sup>1</sup> Read before the American Gastro-enterological Association, May 3, 1920.

<sup>2</sup> Hawk: Practical Physiological Chemistry, 5th edition, p. 355.

<sup>3</sup> Klein: Biochem. Zeit., 1910, xxx, 465.

<sup>4</sup> Mueller: Jour. Biol. Chem., 1910, xxii, 1.

<sup>5</sup> Rothschild and Wilensky: AM. JOUR. MED. SC., vol. clvi, p. 2.

<sup>6</sup> Proc. Assn. Am. Phys., 1920.

of the gall-bladder to withdraw normal salt solution from the hepatic bile and thereby concentrate the latter fluid. There is no reason to believe that cholesterol is changed to cholic acid, a substance participating in the formation of bile salts. The liver probably is the regulator of cholesterol metabolism and maintains the level by excretion through the bile.<sup>7</sup>

Both lecithin and cholesterol assume some role in the transportation and metabolism of fats. The esters of cholesterol are found in the red cells and are practically absent during fasting. The presence of this substance in the red cells probably accounts for the role the latter play in fat metabolism.

The amount of cholesterol normally found in the blood has been variously stated. Baemeister and Havers<sup>8</sup> give 110 to 180 mg. per 100 c.c. and Widal, Weill and Laudat<sup>9</sup> 174 to 195 mg. per 100 c.c. Bloor<sup>10</sup> found the average value for men to be 210 mg. and 230 mg. for women. A wide variety of normals are given by other workers. It is probably fair to say, however, that an upper normal is about 200 mg. per 100 c.c. of blood while the lower level is about 150 mg.

The literature is in accord on the findings of a low blood cholesterol in pernicious anemia which probably has its basis in the diminution of the corpuscular elements to be found in this disease. To beriberi, syphilis, prostration, cachexia and fever are accredited low cholesterol findings, and recently a low blood cholesterol<sup>11</sup> has been found to be of bad prognostic import in nephritis. In non-grave nephritis, arteriosclerosis, obstructive jaundice, diabetes and pregnancy high figures are said to prevail. The literature is by no means in accord as to the constancy of blood cholesterol content in these conditions, and of no disease is this truer than of cholelithiasis. There are those who publish almost constant hypercholesterinemic figures<sup>12</sup> for this disease, while others have had very irregular results.<sup>13 14</sup>

In the winter of 1916-1917, hoping that a determination of the cholesterol content in the blood of gastro-enterological patients would help in diagnosis, especially when the biliary system seemed to be in question, it was planned to examine a series of cases in this way. The Bloor<sup>15</sup> method was employed. Whole blood was used and it was obtained during the morning hours. After a prolonged interruption in the work the number of patients so investigated reached sixty and the number of blood cholesterol readings seventy-five in these cases.

In this group two cases of diabetes showed 160 and 151 mg. from

<sup>7</sup> Rothschild: Proc. New York Path. Soc., December, 1914, N. S., xiv, 229.

<sup>8</sup> Deutsch. med. Wchnschr., 1914, p. 8.

<sup>9</sup> Soc. Biol., 1911, lxiv, 883.

<sup>10</sup> Jour. Biol. Chem., 1916, xxv, 577.

<sup>11</sup> Henes: Arch. Int. Med., April, 1920, xxv, 4.

<sup>12</sup> Henes: Jour. Am. Med. Assn., 1914, lxiii, 149.

<sup>13</sup> Gorham and Meyers: Arch. Int. Med., October, 1917, xx, 4.

<sup>14</sup> Denis: Jour. Biol. Chem., 1917, xxix, 93.

<sup>15</sup> Jour. Biol. Chem., 1916, xxiv, 229.

100 c.c. of blood, while a third case yielded values of 241 and 304 mg. The latter case has a gall-stone history and corresponds in type, but the presence of calculi has never been established. These cases exhibited no acidosis.

Two cases of pernicious anemia showed 139 and 105 mg. Both of these cases presented an achylia gastrica, and it must be assumed that the upper abdominal symptoms here in all probability were gastric in origin. The well-known antihemolytic powers of cholesterol are to be considered in connection with the anemias, and these low figures are interesting in this light. Surroco<sup>16</sup> contends that cholesterol findings in the blood are a measure of the state of the organic defences, and he is not alone in this opinion. Findings below 129 mg. show a weakness in this respect according to this Frenchman and findings above 200 mg. indicate a slow infection of some type. Findings below 100 mg. are of bad prognostic character.

Assuming that the leukocyte count is a measure of organic defence or an index to the presence or absence of infection we found that the low leukocyte count cases in our series averaged 202 mg. of cholesterol while the increased leukocyte cases yielded an average of 220 mg. A case with only a transient gastro-intestinal upset gave findings of 363 mg. and 336 mg. of cholesterol and had but 5000 leukocytes. Our lowest cholesterol finding was in a case with 100 mg., and white cell counts of 9100 and 10,000. None of our low cholesterol cases appeared to be in grave danger nor to be lacking in defence reactions.

Carcinoma and cholesterol, according to some, present an interesting relationship. Luden<sup>17</sup> reports a high cholesterol content in carcinoma and that cholesterol promotes cell multiplication, especially cells of the malignant variety. Our two cases of carcinoma showed readings of 120 and 180 mg.

Four jaundice cases were of the catarrhal variety and yielded 144, 143, 214 and 171 mg., while a single obstruction case showed 330 mg. This accords with the findings of Rothschild and Felsen,<sup>18</sup> who report high findings in the obstructive jaundices.

In gastroduodenal ulcer our findings were 166, 169, 176, 115 and 250 mg. per 100 c.c. of blood. In three of these cases the diagnosis was made clinically while in one the lesion was found at operation and the other showed a filling defect on roentgen-ray examination.

Intestinal stasis cases apparently uncomplicated yielded the following findings: 279, 172, 136, 125, 108, 180, 480 and 125 mg. per 125 mg. per 100 c.c. of blood. In one case three observations were made of 185, 196 and 240 mg.

In this group of 60 cases, 36 were constipated and addicted to the cathartic habit. Their average cholesterol reading was 226 mg. The highest figure was 440 mg. and the lowest one 100 mg. Those

<sup>16</sup> Ann. de la Fac. de Méd., Montevideo, December, 1917.

<sup>17</sup> Jour. Lab. and Clin. Med., December, 1917, p. 3.

<sup>18</sup> Arch. Int. Med., November, 1919, xxiv, 6.

with regular daily movements of the bowels were 16 in number and averaged 183 mg. Three cases with loose, somewhat frequent movements averaged 295 mg.

In cases diagnosed as gastric neuroses of the hypersecretory variety, findings of 160, 185, 200 and 154 mg. were found. One of these cases with 440 mg. was negative in a gastro-intestinal calculus roentgen-ray examination.

A study of the gastric contents of these 60 cases showed that 28 had a high acid curve. Their average cholesterol reading was 218 mg. The normal acid cases numbered 12, with an average reading of 220 mg. Achylia gastrica cases averaged 178 mg. while those with low acid curves showed 184 mg. per 100 c.c. of blood.

In 5 chronic appendicitis cases we found 180, 190, 223, 285 and 318 mg. of cholesterol in 100 c.c. of blood. The last two were operative patients in whom the biliary apparatus was declared negative, but with the appendicular condition there existed widespread adhesions throughout the right abdomen.

The following isolated diagnoses were made in cases with their respective cholesterol readings:

Gall-bladder disease, sino calculus (operative)	149
	195
Rheumatoid arthritis	187
Chronic pancreatitis	248
No abdominal lesion (operative)	286
	147
Visceroptoses (2)	235
	210
Migraine and hypertension	210
Abdominal adhesions (operative)	100

The relationship of cholesterinemia and gall-stones in our cases is shown in this table:

Gall-stones (clinical).	Gall-stones (operative).
200	250
151	
333	190
250	
280	200
316	
Gall-stones (roentgen ray).	Passed stones per bowel.
136	210
200	
220	122
260	
	After passage of stones, calculus roentgen-ray negative.
222	
284	
160	
177	
200	
310	
232	
250	
200	
270	
182	

Bracketed figures represent findings in the same case.

The question of the relationship of cholesterol and gall-stone formation has been much discussed in the literature. For the most part the evidence points to an inconstant and uncertain status. Reiman and Magoun<sup>19</sup> in a study of 60 operative cases found that other upper right abdominal lesions yielded cholesterol figures almost as high as those obtained in stone cases, both averages being above normal. Gorham and Meyers<sup>20</sup> and Denis<sup>21</sup> are in accord that a cholesterol estimation has little clinical and prognostic value in calculus cases.

Obviously there is no reason to assume a hypercholesterinemia in stones of other than cholesterol composition. It must also be true that the precipitation of cholesterol cannot be a uniformly progressive procedure if it depends largely upon an exogenous origin in the blood or bile; that even though a stone were one of hypercholesterinemic origin, findings in the blood would not always show high readings for this lipid. When one subtracts the instances when stone formation has an infection or stasis origin we add still further to the instances when biliary calculi might be present without a hypercholesterinemia. If we consider the weight of gall-stones and add the amount of cholesterol in the bile, together with the length of time required for their formation, it seems only reasonable to assume abnormal conditions of crystallization and precipitation as etiologic factors. The causes of crystallization seem to be found in nuclei of bacteria or epithelial cells.

Whether a hypercholesterinemia can be caused by a lesion of the biliary system in turn due to the presence of stones is uncertain. That lesion could scarcely be anything else than an inflammatory one, and it is well known that stones may exist without inflammation, and inflammation along the biliary tree can be very extensive and severe without calculus formation. The relationship of gall-stones and cholesterol in the blood seems to be a complicated one—one which is intimately related to a complex of food, bile, blood and body tissues—their amount, chemistry, bacteriology and physical properties.

**Summary.** 1. Sixty cases presenting gastro-enterologic aspects were studied for their blood-cholesterol content.

2. Insofar as possible the clinical, roentgen ray and postoperative findings are correlated.

3. The relationship of constipation, hyperacidity and leukocytosis to cholesterol findings are considered.

4. The highest finding was 480 mg., the lowest was 100 mg.

5. Inconstant results were obtained in most of the conditions when more than one case was studied.

6. The figures for cholelithiasis averaged high (228 mg.). Other cases averaged 207 mg., both averages being above the high normal

<sup>19</sup> Surg., Gynec. and Obst., March, 1918, p. 282.

<sup>20</sup> Loc. cit.

<sup>21</sup> Loc. cit.

limit of 200 mg. The highest finding was 316 mg. and the lowest 136 mg. The highest reading in non-calculus cases was 480 mg. and the lowest 100 mg.

7. Inconstant findings were sometimes found when more than one estimation was made in the same case on different days.

**Conclusions.** From our limited studies and an estimate of the literature, blood-cholesterol seems to offer little practical diagnostic help in gastro-enterological cases.

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## A STUDY OF HYPERACIDITY.

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AND

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HYPERACIDITY is a subject which has received an endless amount of discussion. In fact the main portion of this subject has been thoroughly incorporated into the body of clinical medicine without the thorough investigation which the subject deserves. In other words the subjective symptom hyperacidity is a definite clinical entity. Less definite, but none the less fixed in the minds of the medical profession, is the belief that there exists an actual demonstrable titratable acidity. In fact the tremendous amount of clinical work which has been performed on pathologic cases has firmly fixed in the eye of the clinician the fact that high acid figures demonstrate gastric pathology. There was absolutely no evidence at hand to counteract this tendency until a more thorough research into normal gastric activity was carried out. The whole subject, therefore, reverts to the question of a comparison of normal and pathologic findings, and it requires, as a *sine qua non*, an absolute determination of gastric activity and the factors controlling it in health. We must start in with a normal conception before we attempt the interpretation of pathologic data.

We deny that most of the known information on gastric function was obtained on normal individuals, otherwise it is not possible to understand the marked discrepancies which have occurred in this line and which have occasioned so much discussion among gastro-enterologists. An individual with a gastric fistula is not a normal individual; an animal with a Pavlov pouch is not a normal animal; single studies on isolated individuals do not reveal the variations

and normal tendencies which attend gastric digestion. In fact, we know of no series of investigations previous to our own in which a large number of normal individuals were submitted to examinations destined to reveal the whole range and variations of the gastric response to every form of foodstuff.

The results of these investigations, some of which have been published, establishes clearly the following facts, which are of extreme importance in establishing a normal conception of gastric digestion:

Every individual has a characteristic form of gastric digestion.

We would divide this statement into two parts: First, there are apparently three forms of secretory response, all of them found in normal individuals. Secondly, there are three forms of motor response also found in the same individuals. We have already described the three varieties of secretory function as hyper, iso and hyposecretory function. In other words, all individuals belong in one of these three groups, and, as a rule, an individual who shows a hyposecretory response with one type of gastric stimulus (food) will show it with another type of stimulus. About 40 per cent. of normal individuals reveal a response in the hypersecretory group and about 30 per cent. in the iso and hypersecretory groups respectively. An individual in health with conditions equal almost always runs true to type; in disease there may be marked variations, as we shall discuss in later communications. In other words a hypersecretory individual will react in hypersecretory fashion to water, bread, meats and, in fact, the whole line of foodstuffs, while the hyposecretory individual will react in hyposecretory fashion to the same stimuli.

Not only is there a definite form of reaction to a response, but there is also a more or less typical form of motor response, so that we have been able to group our cases into those who from the motor standpoint reacted: (1) rapid evacuation or rapid or quickly emptying stomachs; (2) slowly evacuating stomachs or the hypomotile types; (3) those which empty neither fast nor slow, but, are according to our conceptions, of normal function. We might divide these types into hypermotile, hypomotile and isomotile types, inasmuch as they represent ranges of normal gastric action. In other words, there is unquestionably a large secretory and a large motor range in health which must be thoroughly understood before we draw pathologic interpretations from data which may yield similar figures.

There is no question that exaggerations of almost all of these types may indicate pathology, and the line of demarcation between the end of normal findings and the beginning of pathologic manifestations is exceedingly difficult to define. Furthermore, we know that gastric pathology may exist in the presence of normal secretory and motor function or may convert one type into the other type and